

EXHIBIT C

Expert opinion of Jaime L Sepulveda MD FACOG FACS PRPC
TVT and TVTO devices

I. Credentials and qualifications

My name is Jaime L. Sepulveda-Toro. My attached curriculum vitae reflects my education, training and unique qualifications to render opinions in this case. I graduated from the University of Puerto Rico with a Bachelor in Sciences in 1981 and from the University of Puerto Rico School of Medicine in 1985. I did a Postdoctoral Research Fellowship in Molecular Pharmacology at the same medical school followed by a direct internship and residency training program at the University of Puerto Rico University Hospital. Following completion of my residency program I had an appointment as assistant professor of Obstetrics and Gynecology at the University of Miami School of Medicine where I completed postgraduate education in Pelvic Surgery and Urogynecology. I have been in private practice since 1992.

I am Board Certified in Obstetrics and Gynecology with a subspecialty certification in Female Pelvic Medicine and Reconstructive Surgery. I also hold the only Pelvic Rehabilitation certification available to physicians and surgeons after becoming part of the first class of Certified Pelvic Rehabilitation Practitioners from Herman and Wallace Pelvic Rehabilitation Institute.

I am the Medical Director of the South Miami Medical Arts Surgery Center and Principal Investigator of the Fibroid Registry Research Project of the Center for Women and Infants at South Miami Hospital-Baptist Health, where I hold full privileges for gynecologic surgery. I am the Conference Director for the for the Pelvic Floor Board, a multi-specialty group of physicians specializing in colorectal surgery, physical medicine, urology, neurology, radiology, and urogynecology devoted to the discussion and analysis of challenging pelvic floor conditions seen at our hospital. I am a fellow of the American College of Obstetrics and Gynecology and also a Fellow of the American College of Surgeons. I am a member of the American Urogynecologic Society, the American Urological Association, the International Urogynecologic Association and the International Continence Society.

I have had extensive experience in the care of female urinary incontinence. During my 23 years in practice I have seen the evolution of continence care with and without surgery. I have used native tissue repairs, retropubic and transvaginal suture repairs, autologous slings and synthetic material (specifically polypropylene) for the treatment of stress urinary incontinence. I have had experience in the treatment of complications arising from the use of native tissue, suture repairs, and synthetic and non-synthetic grafts for the surgical treatment of urinary incontinence. My experience has been as a primary surgeon as well as a consultant in treating patients with recurrent and persistent urinary incontinence. My expertise extends to the daily use of diagnostic testing for urinary and fecal incontinence including anorectal physiology testing, anorectal and pelvic floor ultrasound imaging, endoscopic assessment of the bladder and urodynamic testing. I oversee the daily operations in my own clinical facility and of a unit dedicated to the nonsurgical treatment of fecal and urinary incontinence with Pelvic Floor Rehabilitation, Biofeedback and Pelvic Floor Neurostimulation. I devote a significant amount of my day to seeing patients with intractable urge incontinence, voiding dysfunction, urinary retention and recurrent urinary tract infections. I am proficient in the use of neuromodulation for the treatment of voiding dysfunction and urgency incontinence.

I have used and continue to use midurethral slings made of Prolene polypropylene in the care of my patients with stress urinary incontinence. I have accumulated experience with all three generations of midurethral slings - retropubic, transobturator and single incision (TVT, TVTO and TVT Secur). The vast majority of the over two thousand slings I have placed in my practice have been through the transobturator route. I have conducted various types of professional education activities for other surgeons on the use of minimally invasive polypropylene midurethral slings, including TVT and TVTO. These activities encompassed implantation and use, the potential benefits and risks of the device, the IFU and professional education materials, as well as my clinical experience and the medical literature and studies concerning midurethral slings. I have studied the anatomy of this space through the dissection of over 300 cadaver specimens and through MRI imaging of cadavers and patients. I have had over 500 physicians visit my operating room and watch me place a midurethral sling. These visits have been with and without industry sponsorship. I have researched and regularly

read the medical and scientific literature concerning urinary incontinence and its treatment, including the mechanism, efficacy and safety of midurethral slings. Over the years I have spoken to colleagues, scientists, researchers, engineers and anatomists to get a thorough understanding of the mechanism, efficacy and safety of midurethral slings. I have used midurethral slings with and without laser cut Prolene polypropylene mesh graft material. I have counseled my patients on the inherent risks of all continence procedures, including the risk of revision whenever a permanent suture or mesh graft is used.

My education and experience in clinical sciences has allowed me to discriminate the clinical relevance of all information involved in the placement and outcomes of midurethral slings. My background in basic sciences, specifically my formal training in molecular pharmacology including benchwork preparation of cytotoxicity assays, gives me a unique expertise in implants science. My experience working with synthetic midurethral slings, its rare complications and long follow up in my practice also qualifies me to render opinions about the TVT and TVTO.

A list of materials that I have reviewed is attached and includes company documents, the medical literature, and materials relating to midurethral slings including TVT and TVTO. All of my opinions are held to a reasonable degree of medical and scientific certainty. I have also reviewed the reports of experts for the Plaintiffs. I reserve the right to amend this report and my opinions pending receipt of additional materials.

II. Overview and Review of literature

Stress urinary incontinence is a common condition in women. The prevalence of incontinence increases with age and is a major public health concern as our population ages. In the non-elderly population the expectation of cure has increased the utilization of a surgical approach.¹ SUI is defined by the involuntary loss of urine during effort and activity

¹ Nygaard I, Barber MD, Burgio KL, Kenton K, Meikle S, Schaffer J, Spino C, Whitehead WE, Wu J, Brody DJ (2008) Prevalence of symptomatic pelvic floor disorders in US women. JAMA 300:1311–6.

associated with increases in intra-abdominal pressure. The lifetime risk for a female is increased with the physical trauma and denervation of parturition. The physical trauma to the paraurethral structures affects the specific areas of urethral support. Non-surgical approaches are available but are limited by the lack of available qualified providers and the gap in knowledge of evidence based protocols.^{2,3} Midurethral slings have been compared against pelvic floor behavioral therapy and the slings have been found to have a superior cure rate.⁴ The lifetime risk of a woman developing stress incontinence surgery is 13.6%.⁵ As illustrated in the chart below, the number of surgical procedures increased from 37,953 in 1998 to 94,910 in 2007.⁶

² McBride A. Pathophysiology of Stress Urinary Incontinence. *Journal of Pelvic Medicine and Surgery* • Volume 10, Number 1, January/February 2004.

³ Starr JA¹, Drobnis EZ, Lenger S, Parrot J, Barrier B, Foster R. Outcomes of a comprehensive nonsurgical approach to pelvic floor rehabilitation for urinary symptoms, defecatory dysfunction, and pelvic pain. *Female Pelvic Med Reconstr Surg*. 2013 Sep-Oct;19(5):260-5.

⁴ Labrie J, et al. Surgery versus physiotherapy for stress urinary incontinence. *N Engl J Med*. 2013;369:1124-33.

⁵ Wu JM, Matthews CA, Conover MM, Pate, V, Funk MJ. Lifetime risk of stress urinary incontinence or pelvic organ prolapse surgery. *Obstet & Gynecol* 2014; 123:1201-1206.

⁶ Wu JM, Ghandi MP, Shah AD, Shah JY, Fulton RG, Weidner AC. Trends in inpatient urinary incontinence surgery in USA, 1998-2007. *Int Urogynecol J* (2011) 22:1437-1443.

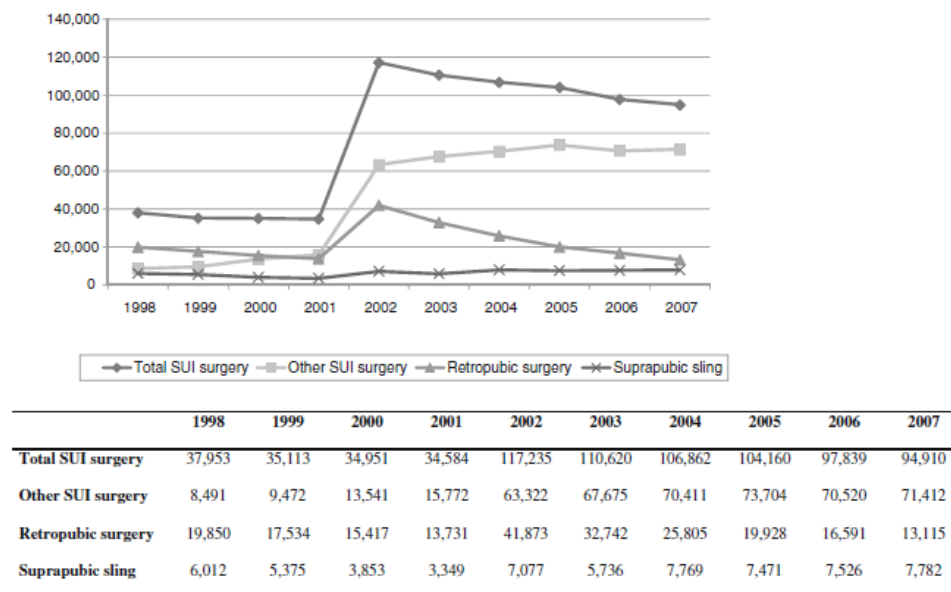


Fig. 1 Total number of stress urinary incontinence inpatient surgeries and different types of SUI surgeries in the USA based on the Nationwide Inpatient Sample data from 1998 to 2007

The earlier primary procedures for urinary incontinence were retropubic suspension of paraurethral tissue with absorbable and/or permanent sutures and the pubovaginal slings. A variety of materials have been used in these procedures, among them Prolene polypropylene (PP) sutures in the retropubic procedures and a variety of autologous, synthetic and animal implants for the pubovaginal slings. All procedures, but in particular these earlier procedures, carried the risk of urinary outlet obstruction, voiding dysfunction, major nerve and vascular injuries, pain, relatively high frequency of revisions and wound healing complications. The recovery from these earlier procedures was burdensome and the cosmetic results at the incisions were unacceptable in cases of seroma formation as well as wound hematoma and excisional hernia. Primary and secondary surgical site infections were also known risks when obtaining fascia from the patient. Understandably the introduction of midurethral sling procedures using PP changed the type of procedure being chosen as the primary surgical approach in a female with SUI.

Burch colposuspensions had earlier been associated with the term “gold standard,” which establishes a clinical benchmark for efficacy for the treatment of SUI. However, studies in the medical literature prior to the arrival of TVT were lacking and of poor quality, making

recommendations about efficacy speculative.⁷ Studies have shown that efficacy of the Burch colposuspension declines after a few years with significant intraoperative and post operative complications, as well as late complications including prolapse development, voiding dysfunction, wound complications, dyspareunia, groin and suprapubic pain.⁸

In 2002, the Burch colposuspension was compared to MUS using TVT and the results proved the noninferiority from one procedure compared to the other, with follow up lasting to five years.⁹ In 2004, laparoscopic Burch colposuspension was compared to TVT with mean follow up of 20.6 months and the results showed shorter operating time for TVT and the TVT also led to greater objective and subjective cure rates for urodynamic stress incontinence than did laparoscopic Burch colposuspension.¹⁰ TVT has been found to have shorter operative time and hospital stay, and higher objective urodynamic cure than laparoscopic Burch colposuspension,¹¹ as well as significantly less de novo urgency, urgency incontinence and time to return to daily

⁷ Black NA, Downs SH. The effectiveness of surgery for stress incontinence in women: a systematic review. *Br J Urol.* 1996 Oct; 78(4):497-510.

⁸ Demirci F, Yucel O, Eren S, Alkan A, Demirci E, Yildirim U. Long-term results of Burch colposuspension. *Gynecol Obstet Invest.* 2001; 51(4):243-7; Chaliha C, Stanton SL. Complications of surgery for genuine stress incontinence. *Br J Obstet Gynaecol.* 1999 Dec; 106(12):1238-45; Alcalay M, Monga A, Stanton SL. Burch colposuspension: a 10-20 year follow up. *Br J Obstet Gynaecol.* 1995 Sep;102(9):740-5. Erratum in: *Br J Obstet Gynaecol* 1996 Mar; 103(3):290; Kjølhed P. Long-term efficacy of Burch colposuspension: a 14-year follow-up study. *Acta Obstet Gynecol Scand.* 2005 Aug; 84(8):767-72; Richter HE, Brubaker L, Stoddard AM, Xu Y, Zyczynski HM, Norton P, Sirls LT, Kraus SR, Chai TC, Zimmern P, Gormley EA, Kusek JW, Albo ME; Urinary Incontinence Treatment Network. Patient related factors associated with long-term urinary continence after Burch colposuspension and pubovaginal fascial sling surgeries. *J Urol.* 2012 Aug; 188(2):485-9.

⁹ Ward K, Hilton P on behalf of the UK and Ireland TVT Trial Group. Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. *BMJ* 2002; 325:67; Ward K, Hilton P on behalf of the UK and Ireland TVT Trial Group. Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5-year follow up. *BJOG* 2008; 115:226-233.

¹⁰ Paraiso MF, Walters MD, Karram MM, Barber MD. [Laparoscopic Burch colposuspension versus tension-free vaginal tape: a randomized trial.](#) *Obstet Gynecol.* 2004 Dec; 104(6):1249-58.

¹¹ Dean N, Herbison P, Ellis G, Wilson D. [Laparoscopic colposuspension and tension-free vaginal tape: a systematic review.](#) *BJOG.* 2006 Dec; 113(12):1345-53.

activities.¹² Given the minimally invasive nature of a TVT, its technical simplicity, the consistency of the product and the high efficacy without the risk of a major abdominal incision, TVT eventually became the gold standard to continence surgeons in the USA.¹³ The placement of a non-absorbable macroporous polypropylene tension free synthetic sling under the mid-urethra is the current standard for the treatment for female SUI. The Type 1 polypropylene mesh, and in particular the Prolene polypropylene mesh used in TVT, has the highest biocompatibility when used to treat SUI and its use predominates current clinical practice.¹⁴

In order to understand the acceptance of TVT as the primary procedure for the cure of urinary incontinence, we need to understand the mechanism of continence, its dearrangement and repair considerations. The urethra is held by a fine arrangement of thin layers of muscle which change as the urethra runs on the anterior wall of the vagina. The urethra is a tubular structure formed by a mucosa and a submucosa. Around the submucosal layer there are two smooth muscle layers, the inner longitudinal and outer circular layers. The inner longitudinal shortens the urethra during micturition while the outer circular maintains the resting tone. Both muscular layers are surrounded by the urogenital sphincter. The striated urogenital sphincter is formed by the urethral sphincter (rhabdomyosphincter), the compressor urethrae and the urethrovaginal sphincter. The rhabdomyosphincter covers 20%-60% of the urethra. The support of the urethra comes from the lateral attachment in its middle portion primarily to the group of muscles and bones formed by the levator muscle groups, the obturator internus muscles and the upper third of the ramus of the pubis. The fibromuscular attachment holding the urethra to the vagina and the fascial support to the arcus tendineous fascia pelvis compresses the urethra during

¹² Ogah J, Cody DJ, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women: a short version Cochrane review. *Neurourol Urodyn*. 2011 Mar; 30(3):284-91.

¹³ Serati M, et al. Surgical treatment for female stress urinary incontinence: what is the gold-standard procedure? *Int Urogynecol J Pelvic Floor Dysfunct*. 2009 Jun; 20(6):619-21.

¹⁴ Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. *Cochrane Database Syst Rev*. 2015 Jul 1; 7:CD006375. [Epub ahead of print] PubMed PMID: 26130017.

straining dividing it into two portions. The resultant increase in urethral pressure generated by the hammock of fibromuscular tissue in the middle of the urethra provides continence during increases in intra-abdominal and pelvic pressures.^{15,16}

I have dissected this area in cadavers extensively and been able to confirm the support to the urethra in this area. I have also confirmed in my dissections the consequences of disconnecting the urethral support and how it translates in hypermobility, not only at the urethrovesical junction but also at midurethra. It is clear to me that the concept of intra-abdominal urethral positioning during straining is physiologically inaccurate. The concept of a hammock supporting the midurethra is scientifically accurate as demonstrated consistently on dissection and imaging of the anterior pelvis and paraurethral tissue.¹⁷ These anatomical considerations were well documented during the description and design of TVTO.

This fine arrangement of support gets its first test at the first vaginal delivery with lower levels of damage after subsequent deliveries. The damage of a vaginal delivery in this area is permanent and is characterized by a torn fibromuscular support to the urethral support mechanism. With impaired support to the urethra, the resistance used to hold urine in the bladder is lower than the force generated by an increase in intra-abdominal pressure and the transmitted pressure to the pelvic floor. Restoration of this broken hammock by placing a durable prosthesis under the urethra forms the scientific rationale to treat stress urinary incontinence with the placement of a synthetic midurethral sling.

The resulting SUI may be complicated by the activation of urethral wetness receptors in the upper urethra. Under normal circumstances

¹⁵ Delancey JOL. Correlative study of paraurethral anatomy. (1986) Obstet and Gynecol: 68;91-97

¹⁶ Brandon CJ, Lewicky-Gaupp C, Larson KA, Delancey JO. Anatomy of the perineal membrane as seen in magnetic resonance images of nulliparous women. Am J Obstet Gynecol. 2009 May;200(5):583

¹⁷ Stein T, DeLancey JOL. Perineal membrane anatomy. (2008). Obstet and Gynecol: 111;3;68-693

these receptors facilitate the micturition process by promoting a bladder contraction. In cases of impaired urethral support the small amount of urine in the upper urethra may promote an uninhibited bladder contraction producing urine loss in larger amounts than typically seen in cases of SUI. Uninhibited bladder muscle activity due to exposure of the receptors in the urethra to urine through a mechanism of stress urinary incontinence may provoke episodes of urgency urinary incontinence, clinically known as mixed urinary incontinence (MUI). Urgency urinary incontinence is seen as part of a continuum of urinary incontinence. SUI and UII may have a common neurological denominator that may persist after the anatomic defect is corrected. The increased functional bladder capacity of cured SUI may precipitate episodes of urgency incontinence. It is not uncommon for patients with MUI to resolve both patterns with a MUS.^{18,19} This was not confirmed for previous continence procedures that concentrated on urethrovesical support instead of the midurethral support provided by a midurethral sling.²⁰ Bladder outlet obstruction as a sequela is significantly lower with tension free TVT slings.

In 1998 the FDA cleared the TVT, the first midurethral sling using Prolene PP without stitching or anchoring to supporting tissue or bone. The technique was novel in the avoidance of the tension provided by an anchoring suture or bony attachments, placement at the midurethra and the use of a synthetic material. However, the configuration of the sling placement and the passage of needles through the space of Retzius were well established by the use of previous pubourethral slings. The use of a synthetic material was most reasonable as the harvesting of autologous grafts increased operative morbidity, and allografts and xenografts had an unpredictable durability and shelf life. The monofilament macroporous Prolene PP also demonstrated useful attributes, tolerability and had a long history of use as both a mesh and a suture.²¹

¹⁸ Cox A, Herschorn S, Lee L. Surgical management of female SUI: is there a gold standard? *Nat Rev Urol.* 2013 Feb; 10(2):78-89.

¹⁹ Jain P, et al. Effectiveness of midurethral slings in mixed urinary incontinence: a systematic review and meta-analysis. *Int Urogynecol J.* 2011; 22:923-932.

²⁰ Tahseen S, Reid P. Effect of transobturator tape on overactive bladder symptoms and urge urinary incontinence in women with mixed urinary incontinence. *Obstet Gynecol.* 2009 Mar; 113(3):617-2

²¹ Falconer C, et al. Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. *Int Urogynecol J Pelvic Floor Dysfunct.* 2001; 12 Suppl 2:S19-23; Petros P. Creating a gold standard surgical

Placement of the sling at midurethra conformed to the newly acquired knowledge of the continence mechanism.²² By 2001 the 5 year data on the use of full length TVT surpassed the cure rates for previously used continence procedures.²³ Studies were carried out in patients with ISD, recurrent prolapse, and mixed urinary incontinence showing effective cure in these various cohorts.²⁴ Cure rates beyond 80% were consistently reproduced, became commonly reported and when the results of a randomized control trial was reported in 2002, the highest level of scientific evidence showed TVT to be equally effective to Burch procedure.²⁵ The study design and methodology applied to the studies was consistently robust and exceeded the scientific scrutiny of previous procedures, which had been adopted for decades without being subjected to frequent and surgically sound trials.²⁶ By 2001 it was reported that with the availability of outpatient surgical procedures for incontinence, the number of women opting for surgical care of stress urinary incontinence increased. Even in the inpatient setting the number of procedures has also increased since 2001. A three-fold increase in the

device: scientific discoveries leading to TVT and beyond: Ulf Ulmsten Memorial Lecture 2014. *Int Urogynecol J*. 2015 Apr; 26(4):471-6.

²² Petros PE, Ulmsten UI. An integral theory and its method for the diagnosis and management of female urinary incontinence. *Scand J Urol Nephrol Suppl*. 1993; 153:1-93; Ulmsten U, et al. An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct*. 1996; 7(2):81-5.

²³ Serati M, Bauer R, Cornu JN, Cattoni E, Braga A, Siesto G, Lizée D, Haab F, Torella M, Salvatore S. TVTO for the treatment of pure urodynamic stress incontinence: efficacy, adverse effects and prognostic factors at 5 years follow-up. *Eur Urol*. 2013 May;63(5):872-8.

²⁴ Rezapour M, Falconer C, Ulmsten U. Tension-Free vaginal tape (TVT) in stress incontinent women with intrinsic sphincter deficiency (ISD)--a long-term follow-up. *Int Urogynecol J Pelvic Floor Dysfunct*. 2001;12 Suppl 2:S12-14; Rezapour M, Ulmsten U. Tension-Free vaginal tape (TVT) in women with recurrent stress urinary incontinence--a long-term follow up. *Int Urogynecol J Pelvic Floor Dysfunct*. 2001;12 Suppl 2:S9-11; Rezapour M, Ulmsten U. Tension-Free vaginal tape (TVT) in women with mixed urinary incontinence--a long-term follow-up. *Int Urogynecol J Pelvic Floor Dysfunct*. 2001;12 Suppl 2:S15-18.

²⁵ Ward K, Hilton P on behalf of the UK and Ireland TVT Trial Group. Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. *BMJ* 2002; 325:67.

²⁶ Black NA, Downs SH. The effectiveness of surgery for stress incontinence in women: a systematic review. *Br J Urol*. 1996 Oct; 78(4):497-510.

total number of procedures for stress urinary incontinence was seen after the introduction of TVT.

With the widespread use of TVT as the primary continence procedure, an unprecedented quality and amount of outcome data became available to surgeons. Scrutiny over efficacy and safety became the subject of multiple publications, with confirmation of consistent efficacy and reproducibility over previously used procedures. TVT and TVTO data has been reported at all levels of evidence and to a depth not previously recorded for any known continence procedure.^{27,28,29,30,31,32,33,34,35,36,37,38}

²⁷ Nilsson CG, Palva K, Rezapour M, Falconer C. Eleven years prospective follow-up of the tension-free vaginal tape procedure for treatment of stress urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct.* 2008 Aug;19(8):1043-7.

²⁸ Liapis A, Bakas P, Creatsas G. Long-term efficacy of tension-free vaginal tape in the management of stress urinary incontinence in women: efficacy at 5- and 7-year follow-up. *Int Urogynecol J Pelvic Floor Dysfunct.* 2008 Nov; 19(11):1509-12.

²⁹ Olsson I, Abrahamsson AK, Kroon UB. Long term efficacy of the tension-free vaginal tape procedure or the treatment of urinary incontinence. A retrospective follow-up 11.5 years post-operatively. *Int Urogynecol J* (2010) 21:679-683

³⁰ Aigmueller T, Trutnovsky G, Tamussino K, Kargl J, Wittmann A, Surtov M, Kern P, Frudinger A, Riss P, Bjelic-Radisic V. Ten-year follow-up after the tension-free vaginal tape procedure. *Am J Obstet Gynecol.* 2011 Nov;205(5):496.e1-5.

³¹ Groutz A, Rosen G, Cohen A, Gold R, Lessing JB, Gordon D Ten-year subjective outcome results of the retropubic tension-free vaginal tape for treatment of stress urinary incontinence.. *J Minim Invasive Gynecol.* 2011 Nov-Dec;18(6):726-9.

³² Serati M, Ghezzi F, Cattoni E, Braga A, Siesto G, Torella M, Cromi A, Vitobello D, Salvatore S. Tension-free vaginal tape for the treatment of urodynamic stress incontinence: efficacy and adverse effects at 10-year follow-up. *Eur Urol.* 2012 May;61(5):939-46.

³³ Heinonen P, Ala-Nissilä S, Kiilholma P, Laurikainen E. Tension-free vaginal tape procedure without preoperative urodynamic examination: long-term outcome. *Int J Urol.* 2012 Nov;19(11):1003-9.

³⁴ Svenningsen R, Staff AC, Schiøtz HA, Western K, Kulseng-Hanssen S. Long-term follow-up of the retropubic tension-free vaginal tape procedure. *Int Urogynecol J.* 2013 Aug; 24(8):1271-8.

³⁵ Nilsson CG, Palva K, Aarnio R, Morcos E, Falconer C. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence *Int Urogynecol J.* 2013 Aug; 24(8):1265-9.

³⁶ Serati M, Sorice P, Bogani G, Braga A, Cantaluppi S, Uccella S, Caccia G, Salvatore S, Ghezzi F. TVT for the treatment of urodynamic stress incontinence: Efficacy and adverse effects at 13-year follow-up. *Neurourol Urodyn.* 2015 Oct 19. doi: 10.1002/nau.22914. [Epub ahead of print] PubMed PMID: 26479043.

The clinical experience, types of complications, frequency of adverse events, surgical technique, and even proficiency per surgeon was widely disseminated at conferences, in journals and textbooks, and became part of board exams and in graduate training. Overall there are over 100 randomized controlled trials that have accumulated and countless more cohort studies on the TVT and TVTO. Several Cochrane Reviews,³⁹ systematic reviews, meta-analyses and practice guidelines⁴⁰ have

³⁷ Novara G, Ficarra V, Boscolo-Berto R, Secco S, Cavalleri S, Artibani W. Tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials of effectiveness. *Eur Urol.* 2007 Sep; 52(3):663-78.

³⁸ Novara G, Galfano A, Boscolo-Berto R, Secco S, Cavalleri S, Ficarra V, Artibani W. Complication rates of tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials comparing tension-free midurethral tapes to other surgical procedures and different devices. *Eur Urol.* 2008 Feb; 53(2):288-308.

³⁹ Ogah J, Cody JD, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. *Cochrane Database Syst Rev.* 2009 Oct 7; (4):CD006375. doi: 10.1002/14651858.CD006375.pub2. Review. PubMed PMID: 19821363; Rehman H, Bezerra CC, Bruschini H, Cody JD. Traditional suburethral sling operations for urinary incontinence in women. *Cochrane Database Syst Rev.* 2011 Jan 19; (1):CD001754. doi: 10.1002/14651858.CD001754.pub3. Review. PubMed PMID: 21249648; Ogah J, Cody DJ, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women: a short version Cochrane review. *Neurourol Urodyn.* 2011 Mar; 30(3):284-91; Lapitan MC, Cody JD. Open retropubic colposuspension for urinary incontinence in women. *Cochrane Database Syst Rev.* 2012 Jun 13; 6:CD002912. doi: 10.1002/14651858.CD002912.pub5. Review. PubMed PMID: 22696331;

⁴⁰ Novara G, Artibani W, Barber MD, Chapple CR, Costantini E, Ficarra V, Hilton P, Nilsson CG, Waltregny D. Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence. *Eur Urol.* 2010 Aug; 58(2):218-38; Dmochowski RR, Blaivas JM, Gormley EA, Juma S, Karram MM, Lightner DJ, Luber KM, Rovner ES, Staskin DR, Winters JC, Appell RA; Female Stress Urinary Incontinence Update Panel of the American Urological Association Education and Research, Inc, Whetter LE. Update of AUA guideline on the surgical management of female stress urinary incontinence. *J Urol.* 2010 May; 183(5):1906-14. doi: 10.1016/j.juro.2010.02.2369. Epub 2010 Mar 29. Review. PubMed PMID: 20303102; revised 2012 at <http://www.auanet.org/common/pdf/education/clinical-guidance/Incontinence.pdf>; Lucas MG, Bosch RJ, Burkhard FC, Cruz F, Madden TB, Nambiar AK, Neisius A, de Ridder DJ, Tubaro A, Turner WH, Pickard RS; European Association of Urology. EAU guidelines on surgical treatment of urinary incontinence. *Eur Urol.* 2012 Dec; 62(6):1118-29, update 2014Apr at <http://uroweb.org/wp->

demonstrated that the TVT and TVTO midurethral slings are as effective or more effective than the Burch colposuspensions and pubovaginal slings while having less morbidity, shorter operating time, less hospital stay, less voiding dysfunction and lower complications.

The use of a single use manufactured device allowed for tracking and reporting into FDA sites not previously available to any other continence procedure. Complications well known to surgeons to be associated with previous procedures found their way through reporting with widely available databases. These complications included hematomas, abscesses, vascular injuries, and bladder and bowel perforations. The reporting was based on the device and manufacturer, and was not by type of procedure. Given the number of procedures, the single use of a manufactured device and the availability of reporting, complications were tracked with unprecedented accuracy (and inaccuracy) and frequency. The MAUDE reporting system allowed an early tracking of complications with a single occurrence of a complication being reported multiple times.⁴¹ The tracking and scrutiny of complications with input of manufacturers, public and physicians was beyond the conventional methods of reporting with any type of continence procedure in the past. It should be clear that the reporting and information retrieval for these complications use a device as a search index, not the condition, indications, added procedures or specific type of procedure. No medical certification of these complications or diagnostic confirmation was required on this report.

Surgical experience made clear that patients treated with TVT had less voiding dysfunction, less wound complications and less retention than the historic numbers from patients treated with pubovaginal slings,

content/uploads/20-Urinary-Incontinence_LR.pdf; Urinary incontinence: the management of urinary incontinence in women. Clinical guidelines CG171. National Institute for Health and Clinical Excellence, September 2013.

<http://guidance.nice.org.uk/CG17>; Schimpf MO, Rahn DD, Wheeler TL, Patel M, White AB, Orejuela FJ, El-Nashar SA, Margulies RU, Gleason JL, Aschkenazi SO, Mamik MM, Ward RM, Balk EM, Sung VW; Society of Gynecologic Surgeons Systematic Review Group. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. *Am J Obstet Gynecol*. 2014 Jul; 211(1):71.e1-71.

⁴¹ Boyles SH, Edwards R, Gregory W, Clark A. Complications associated with transobturator sling procedures. *Int Urogynecol J Pelvic Floor Dysfunct*. 2007 Jan; 18(1):19-22.

needle procedures or open retropubic procedures. Even in cases of voiding dysfunction and urinary retention, quality of life assessment showed an improvement when compared to pre-surgical scores. Tape revisions were in the range of .6% to 7.5%, with the median at 1.1%.⁴² Postoperative urge incontinence was not higher than with previous other procedures and continence cure and improvement was equal or higher.⁴³ There were still complications associated with the implantation of TVT, particularly bladder perforation, which was a known risk with any other needle procedure and there was the risk of exposure of the implant due to a vaginal wound dehiscence. In an analysis of data available on the complications after placement of TVT in numerous studies with follow-up longer than 24 months, the cumulative rates were 1.7% for pelvic hematoma, 3.4% for bladder perforations, 1.1% for vaginal erosion, 0.8% for bladder erosion, 9.7% for urinary tract infections, 15.6% for storage LUTS, 16.1% for voiding LUTS, 4% for clean intermittent catheterization, and 3.2% for reoperations.⁴⁴

Additional studies reporting out of databases have had similar results with low rates of reoperation. For example an analysis of data from US health maintenance organizations reported a nine (9) year rate of urethrolysis or mesh removal of 3.7%⁴⁵. An analysis of data from three Ontario, Canada databases reported a 2.2% rate of sling revision or removal for erosion, fistula, pain, or retention with a cumulative incidence rate of 3.3% at 10 years among women undergoing vaginal mesh-based procedures solely for SUI.⁴⁶ An analysis of Kaiser

⁴² Vervest HA, Bisseling TM, Heintz AP, Schraffordt Koops SE. The prevalence of voiding difficulty after TVT, its impact on quality of life, and related risk factors. *Int Urogynecol J Pelvic Floor Dysfunct.* 2007 Feb;18(2):173-82.

⁴³ Cox A, Herschorn S, Lee L. Surgical management of female SUI: is there a gold standard? *Nat Rev Urol.* 2013 Feb;10(2):78-89.

⁴⁴ Novara G, Galfano A, Boscolo-Berto R, Secco S, Cavalleri S, Ficarra V, Artibani W. Complication rates of tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials comparing tension-free midurethral tapes to other surgical procedures and different devices. *Eur Urol.* 2008 Feb;53(2):288-308.

⁴⁵ Jonsson Funk M, Siddiqui NY, Pate V, Amundsen CL, Wu JM. Sling revision/removal for mesh erosion and urinary retention: long-term risk and predictors. *Am J Obstet Gynecol.* 2013 Jan; 208(1):73.e1-7.

⁴⁶ Welk B, Al-Hothi H, Winick-Ng J. Removal or Revision of Vaginal Mesh Used for the Treatment of Stress Urinary Incontinence. *JAMA Surg.* 2015 Sep; 9:1-9.

Permanente data found that sling loosening or excision for voiding symptoms or urinary retention occurred in 1.2% of patients and excision for vaginal mesh erosion occurred in 0.9% of patients.⁴⁷

In an analysis of Medicare beneficiaries undergoing sling surgery from 2006 to 2008 in hospital outpatient departments and hospital-based ambulatory surgery centers, patients undergoing mesh sling procedures were less likely than patients undergoing non-mesh sling procedures to require management for bladder outlet obstruction (13.9% versus 19.3%, adjusted OR 0.66, 95% CI 0.52-0.85) and were less likely to have a subsequent sling removal and revision or urethrolisis (2.7% versus 4.7%, adjusted OR 0.56, 95% CI 0.35-0.89).⁴⁸

A study examining 3,307 MUS placements at the Cleveland Clinic tertiary care center between 2003 – 2013 showed that 89 patients (2.7%) underwent sling revision with the predominate indication being retention and voiding dysfunction. These data are confounded by concomitant apical suspension which was identified as a risk factor for the need for revision in the retention and voiding dysfunction group. Of the 89 patients who underwent revision, indication for vaginal pain and dyspareunia (7.9%, n=7) as well as groin pain (3.4%, n=3) were very rare when considering the overall risk out of 3,307 sling placements – 0.2% for vaginal pain and dyspareunia (n=7/3,307) and 0.09% for groin pain (n=3/3,307). Additionally, all patients with pain complaints had either partial or complete improvement in symptoms after revision. Revision for mesh erosion was the indication in 21.3% of the 89 patients (n=19) translating into an overall rate of 0.57% in the 3,307 patients. There were no patient characteristics or other variables associated with the need for revision surgery for mesh erosion or pain symptoms.⁴⁹

⁴⁷ Nguyen JN, Jakus-Waldman SM, Walter AJ, White T, Menefee SA. Perioperative complications and reoperations after incontinence and prolapse surgeries using prosthetic implants. *Obstet Gynecol.* 2012 Mar;119(3):539-46.

⁴⁸ Suskind AM, Clemens JQ, Dunn RL, Zhang Y, Stoffel JT, Hollenbeck BK. Effectiveness of mesh compared with nonmesh sling surgery in Medicare beneficiaries. *Obstet Gynecol.* 2013 Sep; 122(3):546-52.

⁴⁹ Unger CA, Rizzo AE, Ridgeway B. Indications and risk factors for midurethral sling revision. *Int Urogynecol J.* 2015 Jul 2. [Epub ahead of print] PubMed PMID: 26134541.

Vaginal wound dehiscence and wound complications are multifactorial and not infrequently seen by vaginal surgeons even without the use of a synthetic material.^{50,51} Wound dehiscence, abdominal wall incisional herniation and exposure of the suture have been described in pubovaginal sling procedures. The vagina wound opens at the site of least resistance, the incision line, under a variety of stressors. Although infection has been theorized to be a factor due to the convention of a “clean contaminated environment,” the evidence does not support that the separation of the incision edges in the vagina is primarily due to infection as infection rates do not correlate with mesh exposure rates with the TVT and TVTO, which use a macroporous, monofilament polypropylene mesh.

Bacteriological analysis of explants have shown flawed collection methodology, lack of prospective design and lacked an explant of TVT Prolene polypropylene specimen. Single reports of TVT infection have been limited to case reports and skin flora contamination with no specifics of culture technique.⁵² Additionally, the presence of bacteria at the surgical site is not equivalent to infection.⁵³ The low risk for infection has been attributed to the plastic coated sheaths during its insertion and the use of macroporous, monofilament polypropylene mesh.^{54,55}

⁵⁰ Albo ME, Richter HE, Brubaker L, Norton P, Kraus SR, Zimmern PE, Chai TC, Zyczynski H, Diokno AC, Tennstedt S, Nager C, Lloyd LK, FitzGerald M, Lemack GE, Johnson HW, Leng W, Mallett V, Stoddard AM, Menefee S, Varner RE, Kenton K, Moalli P, Sirls L, Dandreo KJ, Kusek JW, Nyberg LM, Steers W; Urinary Incontinence Treatment Network. Burch colposuspension versus fascial sling to reduce urinary stress incontinence. *N Engl J Med*. 2007 May 24; 356(21):2143-55.

⁵¹ Schimpf MO, Rahn DD, Wheeler TL, Patel M, White AB, Orejuela FJ, El-Nashar SA, Margulies RU, Gleason JL, Aschkenazi SO, Mamik MM, Ward RM, Balk EM, Sung VW; Society of Gynecologic Surgeons Systematic Review Group. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. *Am J Obstet Gynecol*. 2014 Jul; 211(1):71.e1-71.

⁵² Boulanger L, Boukerrou M, Rubod C, Collinet P, Fruchard A, Courcol RJ, Cosson M. Bacteriological analysis of meshes removed for complications after surgical management of urinary incontinence or pelvic organ prolapse. *Int Urogynecol J Pelvic Floor Dysfunct*. 2008 Jun; 19(6):827-31.

⁵³ Culligan P, Heit M, Blackwell L, Murphy M, Graham CA, Snyder J. Bacterial colony counts during vaginal surgery. *Infect Dis Obstet Gynecol*. 2003; 11(3):161-5..

⁵⁴ Ogah J, Cody JD, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. *Cochrane Database Syst Rev*. 2009 Oct 7; (4):CD006375.

Other factors contributing to exposure of the tape include the formation of a hematoma at dissection sites. As a hematoma of significant volume is accumulated under the vaginal epithelium, the volume creates enough pressure to find a course and drain through the incision. The incision is being held by absorbable sutures and progressive loss of tensile strength is expected from the moment the sutures are placed. Once the incision is open the exposure of the implant is evident. The limited dissection required for implantation of these devices decreases the potential risk of wound dehiscence. The role of mechanical disruption of the wound at the suture line, smoking, and deleterious effect of a catheter in the wound healing process are important factors to consider in the etiology of a tape exposure.

The tape used in a single use manufactured device like TVT and TVTO is not placed under the same drag as a needle procedure. The sheath allows for surgical control without stretching or tension at adjustment. When placed per the IFU, the risk of deformation of the tape is reduced. The use of the plastic sheath translates clinically into a limited exposure to the vaginal environment and facilitates the adjustment of the sling. The use of a surgical instrument to act as a spacer between the suburethral tissue and the sling has been advocated universally and has become part of the IFU for TVT and TVTO to avoid uncontrolled tensioning. It is a maneuver that has been used to control adjustment and tensioning in essentially all full length incontinence procedures, and even in periurethral suspension procedures to avoid overcorrection, voiding dysfunction and urinary retention.⁵⁶

While there is a risk of urinary tract infection following incontinence surgery, the rate following TVT and TVTO placement is lower than with the Burch colposuspension. Analysis of the two year results from the UITN SISTER and TOMUS studies show the rates of UTI were highest

⁵⁵ Cosson M, Debodinance P, Boukerrou M, Chauvet MP, Lobry P, Crépin G, Ego A. Mechanical properties of synthetic implants used in the repair of prolapse and urinary incontinence in women: which is the ideal material? *Int Urogynecol J Pelvic Floor Dysfunct.* 2003 Aug; 14(3):169-78; discussion 178.

⁵⁶ Significance of tension in tension-free mid-urethral sling procedures: a Paick JS, Oh JG, Shin JW, Kim SW, Ku JH. preliminary study. *Int Urogynecol J Pelvic Floor Dysfunct.* 2007 Feb; 18(2):153-8.

with the pubovaginal sling (48%) and Burch procedure (32%)⁵⁷, and lowest with the TVT (17%) and TVTO (11%).⁵⁸ And, from a basic epidemiologic standpoint, urinary tract infections are common in women.

The complications of midurethral slings including TVT and TVTO were well studied, disseminated and published independently from Ethicon in numerous cohort series, randomized controlled trials, various meta-analyses and professional organization guidelines and reviews. These complications were comparable to other continence procedures and lower on multiple reports. The one complication that most surgeons feared was a rare but serious bowel perforation at the time of the passage of needles through the retropubic space. As surgeons, we were familiar with the unusual occurrence of bowel perforations during placement of needles for continence procedures as well as the placement of suprapubic catheters. A bowel perforation was rare (less than 0.5%) but always a feared possibility in a retropubic continence procedure. The prevention of adverse events became the subject of articles on expert series and surgical technique bulletins in various professional society journals.

In 2001 Delorme described the placement of a midurethral sling with a transobturator approach by placing insertion needles from the outside in. Dr. de Leval described an approach by inserting the needles from inside out.⁵⁹ In both procedures the adjustment of the sling under the midurethra was done by pulling from the inside out. Understandably when both procedures were compared the cure rates were not

⁵⁷ Albo ME, Richter HE, Brubaker L, Norton P, Kraus SR, Zimmern PE, Chai TC, Zyczynski H, Diokno AC, Tennstedt S, Nager C, Lloyd LK, FitzGerald M, Lemack GE, Johnson HW, Leng W, Mallett V, Stoddard AM, Menefee S, Varner RE, Kenton K, Moalli P, Sirls L, Dandreo KJ, Kusek JW, Nyberg LM, Steers W; Urinary Incontinence Treatment Network. Burch colposuspension versus fascial sling to reduce urinary stress incontinence. *N Engl J Med*. 2007 May 24;356(21):2143-55. Epub 2007 May 21. PubMed PMID: 17517855.

⁵⁸ Albo ME, Litman HJ, Richter HE, Lemack GE, Sirls LT, Chai TC, Norton P, Kraus SR, Zyczynski H, Kenton K, Gormley EA, Kusek JW; Urinary Incontinence Treatment Network. Treatment success of retropubic and transobturator mid urethral slings at 24 months. *J Urol*. 2012 Dec;188(6):2281-7. doi: 10.1016/j.juro.2012.07.103. Epub 2012 Oct 22. PubMed PMID: 23083653; PubMed Central PMCID: PMC4367868.

⁵⁹ ETH.MESH.00823793

different.⁶⁰ Not only were the cure rates similar, they were not different from the retropubically placed TVT.^{61,62}

Statistical and clinical equivalence of the TVTO compared to TVT was demonstrated in a randomized equivalence trial. The overall number of serious adverse effects, voiding dysfunction, bladder perforation, and urinary tract infections was more common after the placement of retropubic sling in comparison to the TVTO. Leg weakness and groin numbness was more frequent after the TVTO procedure but required no intervention.⁶³

Complications from the transobturator approach were even lower than with retropubic TVT. The transobturator approach showed a higher frequency of early postoperative pain as the insertion needle went through the superficial muscles of the leg. This complication is most often transient and managed with medication. Several long term TVTO studies showed low rates of complications including leg pain and exposure.⁶⁴ In a recent five year multicenter randomized controlled trial

⁶⁰ Ogah J, Cody DJ and Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women : a short version Cochrane review. (2011) *Neurol and Urodyn* 30 :284-291

⁶¹ Palva K, Rinne K, Aukee P, Kivelä A, Laurikainen E, Takala T, Valpas A, Nilsson CG A randomized trial comparing tension-free vaginal tape with tension-free vaginal tape-obturator: 36-month results. *Int Urogynecol J*. 2010 Sep; 21(9):1049-55.

⁶² Sung VW, Schleinitz MD, Rardin CR, Ward RM, Myers DL. Comparison of retropubic vs transobturator approach to midurethral slings: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2007 Jul; 197(1):3-11.

⁶³ Richter HE, Albo ME, Zyczynski HM, Kenton K, Norton PA, Sirls LT, Kraus SR, Chai TC, Lemack GE, Dandreo KJ, Varner RE, Menefee S, Ghatti C, Brubaker L, Nygaard I, Khandwala S, Rozanski TA, Johnson H, Schaffer J, Stoddard AM, Holley RL, Nager CW, Moalli P, Mueller E, Arisco AM, Corton M, Tennstedt S, Chang TD, Gormley EA and Litman HJ for the Urinary Incontinence Treatment Network. Retropubic versus Transobturator Midurethral Slings for Stress Incontinence. *N Engl J Med* 2010; 362(22); 2066-76.

⁶⁴ Tommaselli GA, D'Afiero A, Di Carlo C, Formisano C, Fabozzi A, Nappi C. Tension-free vaginal tape-obturator and tension-free vaginal tape-Secur for the treatment of stress urinary incontinence: a 5-year follow-up randomized study. *Eur J Obstet Gynecol Reprod Biol*. 2015 Feb; 185:151-5; Tommaselli GA, Di Carlo C, Formisano C, Fabozzi A, Nappi C. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. *Int Urogynecol J*. 2015 May 20. [Epub ahead of print] PubMed PMID: 25990203; Athanasiou S, Grigoriadis T, Zacharakis D, Skampardonis N, Lourantou D,

comparing TVT and TVTO, high cure rates and patient satisfaction were seen with both. The objective cure rate was 84.7% in the TVT group and 86.2% in the TVTO group and subjective treatment satisfaction was 94.2% in the TVT group and 91.7% in the TVTO group, with no difference between groups. Significant improvements were seen in quality of life for both groups. Additionally, 84% of patients were cured of their preoperative urgency symptoms. Complication rates were low, with no difference between groups, and none of the patients had any sign of tissue reaction, erosion, or tape protrusion at their 5-yr follow-up.⁶⁵

It became evident that specialized knowledge of the obturator site and the anatomy and relationship of the vascular, muscular and nerve studies, were required for a reproducible and safe obturator procedure. Cadaveric dissection showed the distance to the obturator neurovascular bundle ranging from 1.2-1.5 cm for TVTO and 2.2cm-2.5 cm for the outside in approach.⁶⁶ A neurological explanation for pain from an obturator nerve injury was formulated but not reproduced by objective studies - electromyography or MRI. If injury to the obturator nerve was to be explained, atrophy of the muscles innervated by the obturator nerve would have been expected by MRI imaging. Not only is this confirmation of nerve injury non-existing, electromyographic studies are also lacking. The reports at the MAUDE database were with one out of

Antsaklis A. Seven years of objective and subjective outcomes of transobturator (TVT-O) vaginal tape: why do tapes fail? *Int Urogynecol J.* 2014 Feb; 25(2):219-25. doi: 10.1007/s00192-013-2186-8. Epub 2013 Jul 27; Laurikainen E, Valpas A, Aukee P, Kivelä A, Rinne K, Takala T, Nilsson CG. Five-year results of a randomized trial comparing retropubic and transobturator midurethral slings for stress incontinence. *Eur Urol.* 2014 Jun;65(6):1109-14; Serati M, Bauer R, Cornu JN, Cattoni E, Braga A, Siesto G, Lizée D, Haab F, Torella M, Salvatore S. TVT-O for the treatment of pure urodynamic stress incontinence: efficacy, adverse effects, and prognostic factors at 5-year follow-up. *Eur Urol.* 2013 May; 63(5):872-8; Cheng D, Liu C. Tension-free vaginal tape-obturator in the treatment of stress urinary incontinence: a prospective study with five-year follow-up. *Eur J Obstet Gynecol Reprod Biol.* 2012 Apr; 161(2):228-31; Liapis A, Bakas P, Creatsas G. Efficacy of inside-out transobturator vaginal tape (TVTO) at 4 years follow up. *Eur J Obstet Gynecol Reprod Biol.* 2010 Feb; 148(2):199-201.

⁶⁵ Laurikainen E, Valpas A, Aukee P, Kivelä A, Rinne K, Takala T, Nilsson CG. Five-year results of a randomized trial comparing retropubic and transobturator midurethral slings for stress incontinence. *Eur Urol.* 2014 Jun;65(6):1109-14.

⁶⁶ Zahn CM, Siddique S, Hernandez S, Lockrow EG. Anatomic comparison of two transobturator tape procedures. *Obstet Gynecol.* 2007 Mar; 109(3):701-6.

two reported obturator injuries reported to have been confirmed by neurological consultation.⁶⁷

From a surgeon's perspective, the placement of the transobturator sling from the inside out offered a proven efficacious continence procedure, a precise placement at midurethra of a well studied macroporous Prolene polypropylene tape, and a well-tolerated procedure with less blood loss, less urinary retention and no risk for bladder or bowel perforation. The proximity to the obturator neurovascular bundle was most frequently a failure to orient the device from 45 degrees to 90 degrees as specified by the IFU.⁶⁸ The change in angle after the entering of the obturator membrane, in close proximity to the posteromedial aspect of the upper third of the descending pubic ramus, is a critical step in inserting the trajectory of the tape through the tendinous attachment of the obturator and adductor muscles and not through the proximity of the neurovascular bundle. A recent systematic review and metaanalysis confirms that transobturator slings are not inferior to retropubic slings and there was not a significant difference seen in postoperative pain.⁶⁹

In 2008, the FDA published a Public Health Notice concerning surgical pelvic mesh. This Public Health Notice discussed both potential complications and counseling of patients. Pelvic floor surgeons using mesh to treat SUI, such as TVT and TVTO, would be aware of and would be expected to know of the Notice, the potential complications, as well as their severity and need for reoperation discussed therein, and recommendations made. In 2013 the FDA published an updated notice concerning the SUI meshes like TVT and TVTO -- Considerations about Surgical Mesh for SUI. This notice identifies that the safety and effectiveness of multi-incision slings like TVT and TVTO is well-established in clinical trials that followed patients for up to one-year and that longer follow-up data is available in the literature.

⁶⁷ Complications associated with transobturator sling procedures. Boyles SH, Edwards R, Gregory W, Clark A. *Int Urogynecol J Pelvic Floor Dysfunct.* 2007 Jan; 18(1):19-22.

⁶⁸ ETH.MESH.02340905

⁶⁹ Tommaselli GA, Di Carlo C, Formisano C, Fabozzi A, Nappi C. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. *Int Urogynecol J.* 2015 May 20. [Epub ahead of print] PubMed PMID: 25990203.

There is a high degree of statistically valid evidence on the use of TVT and TVTO demonstrating their efficacy and safety. Hundreds of clinical studies, randomized controlled trials, systematic reviews and meta-analyses, and clinical guidelines, including numerous studies with a duration of 5, 10 and 15 plus years have been published and widely available to all surgeons. The 2013 FDA updated notice reminded surgeons of complications which we were all aware of and would be expected to know. The FDA correctly observed that with the exception of mesh exposure, these complications can occur following a non-mesh surgical repair for SUI. And as earlier stated, wound complications can occur with following a non-mesh surgical repair for SUI.

Each TVT and TVTO device is accompanied by an IFU. I have reviewed the TVT and TVTO IFUs and find them adequate and complete for its use in the operating room by the intended users. As a surgeon, I understand that the IFU is not a comprehensive guide for the surgical treatment of SUI. The IFU builds on the knowledge that we as pelvic floor surgeons have acquired through prior education, instruction and experience. The IFU adequately informs surgeons of the use of the TVT and TVTO and the potential risks and complications.

I have conducted numerous activities for the purpose of professional education including surgical anatomy laboratories with the use of models and cadavers, consensus conferences among experienced users, surgical demonstrations in the operating room and didactic lectures. All these activities offer the opportunity to address the complications and details of the surgery along with the interpretation of the IFU. The professional education activities provided the opportunity to exchange knowledge among surgeons. Ethicon's professional education, which is recommended in the IFU, supplements the IFU.

I use the TVT and TVTO patient brochures in my practice. Both allow a patient to construct a base to be used in the conversation about the procedure. These brochures are not meant to supplant the informed consent process, but rather are a resource for additional information and mention complications inherent to continence procedures. The IFU, patient brochure, professional education, medical literature, and the 2008 FDA Public Health Notification discuss potential complications to

be addressed in the informed consent process for a MUS and were available to surgeons. These instruments have been used and continue to be used by trained pelvic surgeons as a standard of practice in the counseling of their patients.

There have been several claims made by the Plaintiff's experts regarding the mesh and the device which in my opinion are incorrect and lack scientific support. Moreover, the large volume of clinical data on the TVT sling including the highest level of evidence and long term data are inconsistent with these theories.

The biomechanical properties of slings have been studied using a variety of models adapted from the testing of fabrics, textiles and sutures. None of the models have been able to replicate the behavior of the sling in the host with a level of scientific accuracy and validity that could be correlated with outcomes data. The use of dynamometers and standard biomechanical testing place emphasis on the physical characteristics of a Prolene polypropylene sling but leaves the interaction with the host to theoretical assumptions.

The monofilament knitted Prolene polypropylene TVT sling has pores which are macroporous (over 75 microns). A pore size above 75 microns allows for the migration of neutrophils (9-12 microns) and mature inflammatory cells (20 microns), considering that most studies are on explants. The clinical data show that the pore size, weight, and construct of the TVT mesh is optimal for treating urinary incontinence.

Explants from humans get forces well beyond the intended force for a sling procedure; explants are in essence useless in the evaluation of the host-graft interaction. Explanted material is the subject of mechanical stressors beyond its limits and has no clinical predictive value.

A claim has been made that the mechanically cut sling is a defective product. There was no data (and still is none) indicating that modification from mechanical to laser cutting would result in any potential effects on clinical outcomes. A number of parameter measurements were used to compare the physical characteristics of MCM and LCM. Elongation testing analysis and flexural rigidity in machine and cross direction were measured without statistically

significant differences. Review of internal documents from Ethicon regarding the medical interpretation of biomechanical engineering test data shows no difference on the product physical characteristics.⁷⁰

A communication regarding the photographic difference at 50% elongation was circulated to marketing and sales personnel.⁷¹ Surgically, an elongation at 50% is well beyond the forces used in the operating room. Moreover, when the sling is implanted it is covered by the sheath which distributes the forces across the sheath protecting the sling. Notably the bench top testing does not utilize the tape with the sheath on it. If it did, the tape would not move or stretch within the protective sheath. Additionally the trocars are also not included in the bench top testing. The use of the trocars provides for the smooth placement of the tape and sheath which follow the trocars through the tissue.

Both mechanical cut mesh and laser cut mesh in the TVT and TVTO behave the same in vivo and the data show no significant difference in efficacy or complication rates in studies that were performed before and after 2007 when laser cut mesh was utilized. Instead, there is a consistency in the data regardless of the type of cutting to the edges of the macroporous Prolene polypropylene tape. The long term data on TVT and TVTO are also inconsistent with a theory that mechanical cut TVT tape is defective. This evaluation is in agreement with my clinical observations in the operating room using mechanical cut mesh and laser cut mesh.

The use of machines to evaluate a mesh implant gives information about the consistency of a product to a manufacturer but it has the limitation of not having a complete assessment of all variables in vivo. The host graft interaction has been previously evaluated and submitted to the FDA; tolerability and safety has been proven by the predicate device and graft, in this case the TVT Prolene polypropylene mesh tape.^{72,73} The in vivo animal model studies with mechanically cut PP show the best tissue

⁷⁰ ETH.MESH.01784825

⁷¹ ETH.MESH.08334244

⁷² ETH.MESH.08476210-6342

⁷³ Falconer C, Söderberg M, Blomgren B, Ulmsten U. Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. *Int Urogynecol J Pelvic Floor Dysfunct.* 2001;12 Suppl 2:S19-23.

integration and mechanical performance when compared to Vicryl, Vypro, Mersilene and Prolene soft. Most importantly, the effect of cicatrization on lengthening and resistance favors the use of mechanically cut PP as a sling material.

Particle loss was found to be higher in MCM than in LCM. The loss of particles is at the edge of the mesh implant. These are minute particles measured independently at 0.179 mm. Surgically this is of no significance. There is no evidence, published or clinical, that could be associated to differences in efficacy or tolerability. If any particles were seen at placement, the particles would make no difference in the placement or adjustment of the sling. The size of these particles is significantly smaller when compared to the variety of devices used for hemostasis and suturing. Overall the data does not show any clinically significant difference between mechanical versus laser cut mesh. Moreover, in the hypothetical visco-hyperelastic model for vaginal tissue with a low vaginal stiffness index, the use of a compliant mesh sling, regardless of its edges, may decrease the rate of obstructive voiding dysfunction.

Surgeons have various preferences and the mechanical cut TVT mesh has been in use and studied for almost two decades. The mechanical and laser cut TVT and TVTO are within the standard of care and none of the pertinent SUI guidelines and analyses distinguish efficacy or safety of the devices based on the way the edges of the mesh are cut, nor do they support the theories espoused by the Plaintiff's experts.⁷⁴

The use of Prolene polypropylene in TVTO followed its use in over 500,000 cases of retropubic TVT for suburethral slings. A Medline search for sarcoma and polypropylene does not yield a single case of sarcoma or malignancy due to the use of polypropylene material in humans. MSDS and rat studies reporting sarcoma formation after implantation of polypropylene discs and powder are not transferable to

⁷⁴ 2015 Cochrane Review; 2014 AUGS/SUFU Statement; 2014 ACOG Statement; 2014 IUGA Statement; 2014 SGS Guidelines; 2013 AUA Position Statement; 2013 NICE Clinical Guideline 171; 2013 ICS SUI Fact Sheet; 2012 EAU Guideline; 2012 AUA Guideline; Cox 2013 Review; 2011 Cochrane Review; Novara 2010 metaanalysis.

humans.⁷⁵ Raw materials as referenced in MSDS are not implanted in humans. Instead they are processed and formulated. The same is true for pharmaceuticals. The available data does not show any causal link between polypropylene and cancer.^{76, 77, 78, 79}

There is no evidence of human cytotoxicity. Cytotoxicity assessment of the Ulmsten Prolene polypropylene sling using the ISO Elution method showed cell lysis and toxicity; however, this was not confirmed by the ISO Agarose Diffusion method.^{80,81} Cytotoxicity assessment of normal production Prolene polypropylene using the Agarose Overlay Method and Extraction Filter Method showed no cytotoxicity.^{82,83} An exploratory cytotoxicity assessment of unwashed non-sterile Prolene polypropylene mesh raw material using the ISO Elution method did not show cytotoxicity or cell lysis.^{84,85} Normal production Prolene polypropylene has not shown cytotoxicity at drug elution, ISO Agarose overlay method, or with the extraction /filter paper method. All testing methods use a monolayer of L-929 mouse fibroblast cells.^{86,87}

⁷⁵ King AB, Goldman HB. Current controversies regarding oncologic risk associated with polypropylene midurethral slings. *Curr Urol Rep*. 2014 Nov;15(11):453. doi: 10.1007/s11934-014-0453-y. PubMed PMID: 25234187.

⁷⁶ Moalli P, Brown B, Reitman M, Nager C. Polypropylene mesh: evidence for lack of carcinogenicity. *Int Urogynecol J*. 2014 May;25(5):573-6.

⁷⁷ March 12, 2014 AUGS-SUFU Frequently Asked Questions by Providers: Mid-urethral slings for Stress Urinary Incontinence. <http://www.augs.org/p/bl/et/blogid=16&blogaid=194>

⁷⁸ King AB, Zampini A, Vasavada S, Moore C, Rackley RR, Goldman HB. Is there an association between polypropylene midurethral slings and malignancy? *Urology*. 2014 Oct;84(4):789-92.

⁷⁹ Linder BJ, Trabuco EC, Carranza DA, Gebhart JB, Klingele CJ, Occhino JA. Evaluation of the local carcinogenic potential of mesh used in the treatment of female stress urinary incontinence. *Int Urogynecol J*. 2016 Feb 10. [Epub ahead of print] PubMed PMID: 26864666.

⁸⁰ ETH.MESH.08476311

⁸¹ ETH.MESH.08476314

⁸² ETH.MESH.08476315

⁸³ ETH.MESH.08476316

⁸⁴ ETH.MESH.08476317

⁸⁵ ETH.MESH.08476318

⁸⁶ ETH.MESH.08476315

⁸⁷ ETH.MESH.08476316

Polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants.⁸⁸ In recent years, concerns regarding implanted polypropylene degradation have been raised as a result of very high magnification images that show portions of some explanted synthetic meshes with “cracked” surfaces.⁸⁹ These case reports and case series of explants lack reliability and one cannot draw any causal inference from them or extrapolate their reported SEM findings to the larger population. In the referenced Clave study there were several methodologic flaws. Moreover, only a minority of the explants were reported to have surface cracking and degradation and oxidation were not shown on chemical analyses. While the purported surface changes were hypothesized to lead to adverse clinical outcomes, these hypotheses have not been confirmed. Nor are these hypotheses supported by the extensive peer-reviewed literature related to the TVT and TVTO slings. Prospective studies have followed patients with implanted with TVT at long term as earlier referenced and show excellent durability and safety of TVT and TVTO.

The medical literature including over 1,000 studies, meta-analyses and systematic reviews, and the endorsement of the TVT mesh by the pertinent medical societies do not support that the mesh is cytotoxic, that it degrades or leads to a harmful inflammatory response in humans. To the contrary, the use of macroporous Type 1 Prolene polypropylene in TVT is the most biocompatible for use to treat urinary incontinence and is the preferred material for this intended use.^{90,91,92,93} The high degree of efficacy, the low rates of complications and the very low rates

⁸⁸ AUGS-SUFU FAQs by Providers on Mid-urethral Slings for SUI, 2014.

⁸⁹ Clavé A, Yahi H, Hammou JC, Montanari S, Gounon P, Clavé H. Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. *Int Urogynecol J*. 2010 Mar;21(3):261-70.

⁹⁰ Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. *Cochrane Database Syst Rev*. 2015 Jul 1; 7:CD006375. [Epub ahead of print] PubMed PMID: 26130017

⁹¹ NICE Clinical Guideline 171- Urinary Incontinence: The management of urinary incontinence in women. Sept. 2013.

⁹² Ogah J, Cody DJ, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women: a short version Cochrane review. *Neurourol Urodyn*. 2011 Mar; 30(3):284-91.

⁹³ AUGS-SUFU Position Statement on Mesh Midurethral Slings for SUI. January 3, 2014.

of reoperation based on the highest level of scientific data are inconsistent with and refute the Plaintiff's experts' claims and hypotheses, which in essence are speculation and conjecture based on irrelevant, unreliable and/or low level data.

Overall the data show that the TVT and TVTO slings used to treat urinary incontinence are safe and effective. They are not defective and instead these well studied slings have significant usefulness to surgeons in the field.

Midurethral slings like TVT and TVTO are the standard of care for the surgical management of urinary stress incontinence.^{94, 95, 96} Like the TVT, long term data continues to support the use of TVTO with proven safety and efficacy.⁹⁷ Use of the device is the surgery of choice for urologists

⁹⁴ Schimpf MO, Rahn DD, Wheeler TL, Patel M, White AB, Orejuela FJ, El-Nashar SA, Margulies RU, Gleason JL, Aschkenazi SO, Mamik MM, Ward RM, Balk EM, Sung VW; Society of Gynecologic Surgeons Systematic Review Group. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. *Am J Obstet Gynecol.* 2014 Jul; 211(1):71.e1-71; Cox A, Herschorn S, Lee L. Surgical management of female SUI: is there a gold standard? *Nat Rev Urol.* 2013 Feb; 10(2):78-89; Dmochowski RR, Blaivas JM, Gormley EA, Juma S, Karram MM, Lightner DJ, Luber KM, Rovner ES, Staskin DR, Winters JC, Appell RA; Female Stress Urinary Incontinence Update Panel of the American Urological Association Education and Research, Inc, Whetter LE. Update of AUA guideline on the surgical management of female stress urinary incontinence. *J Urol.* 2010 May; 183(5):1906-14; Novara G, Artibani W, Barber MD, Chapple CR, Costantini E, Ficarra V, Hilton P, Nilsson CG, Waltregny D. Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence. *Eur Urol.* 2010 Aug; 58(2):218-38.

⁹⁵ Labrie J, et al. Surgery versus physiotherapy for stress urinary incontinence. *N Engl J Med.* 2013; 369:1124-33.

⁹⁶ NICE Clinical Guideline 171- Urinary Incontinence: The management of urinary incontinence in women. Sept. 2013.

⁹⁷ Tommaselli GA, Di Carlo C, Formisano C, Fabozzi A, Nappi C. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. *Int Urogynecol J.* 2015 May 20. [Epub ahead of print]; Athanasiou S, Grigoriadis T, Zacharakis D, Skampardonis N, Laurantou D, Antsaklis A. Seven years of objective and subjective outcomes of transobturator (TVTO) vaginal tape: why do tapes fail? *Int Urogynecol J.* 2014 Feb; 25(2):219-25. doi: 10.1007/s00192-013-2186-8; Laurikainen E, Valpas A, Aukee P, Kivelä A, Rinne K, Takala T, Nilsson CG. Five-year results of a randomized trial comparing retropubic and transobturator midurethral slings for stress incontinence.

and urogynecologists.^{98,99,100} My opinions are supported by the highest degree of medical evidence available to the practicing pelvic surgeon and continence specialists.¹⁰¹ My surgical practice and professional opinions are based on scientific evidence, experience and a confirmatory consensus of the medical societies representing those dedicated to the care of women with urinary incontinence.^{102,103}

The pertinent societies continue to analyze the voluminous data which support TVT and TVTO. The November 2015 ACOG and AUGS Practice Bulletin 155 Urinary Incontinence in Women recommends the TVT and TVTO because it is safe and effective and less invasive and morbid than alternatives.¹⁰⁴ The following conclusions and recommendations, with

Eur Urol. 2014 Jun; 65(6):1109-14; Serati M, Bauer R, Cornu JN, Cattoni E, Braga A, Siesto G, Lizée D, Haab F, Torella M, Salvatore S. TVTO for the treatment of pure urodynamic stress incontinence: efficacy, adverse effects, and prognostic factors at 5-year follow-up. Eur Urol. 2013 May; 63(5):872-8.

⁹⁸ Clemons JL. Impact of the 2011 FDA transvaginal mesh safety update on AUGS members' use of synthetic mesh and biologic grafts in pelvic reconstructive surgery. Female Pelvic Med Reconstr Surg 2013; 19:191-98. (>95% usage of MUS)

⁹⁹ Chughtai BI, Midurethral Sling Is the Dominant Procedure for Female Stress Urinary Incontinence: Analysis of Case Logs From Certifying American Urologists. Urology. 2013 Oct 15. (significant increase in MUS usage and significant reduction in older procedures to treat SUI)

¹⁰⁰ Nager, C.W., et al., A randomized trial of urodynamic testing before stress-incontinence surgery. N Engl J Med 2012; 366:1987-97 (full length MUS was the choice procedure for 93% of surgeons in the UITN).

¹⁰¹ Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015 Jul 1;7:CD006375. [Epub ahead of print] PubMed PMID: 26130017.

¹⁰² AUGS-SUFU Position Statement on Mesh Midurethral Slings for SUI. January 3, 2014; IUGA Position Statement on Mid-Urethral Slings for Stress Urinary Incontinence, July 2014. ICS Fact Sheet Stress Urinary Incontinence, July 2013; AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence, October 2013

¹⁰³ Lucas MG, EAU Guidelines on Surgical Treatment of Urinary Incontinence. Eur Urol. 2012; 62:1118-29.

¹⁰⁴ American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology and the American Urogynecologic Society. Practice Bulletin No. 155: Urinary Incontinence in Women. Obstet Gynecol. 2015 Nov;126(5):e66-81. PubMed PMID: 26488524; Practice Bulletin No. 155 Summary: Urinary Incontinence in Women. Obstet Gynecol. 2015 Nov;126(5):1120-2.

which I agree, were determined to be based on good and consistent scientific evidence (Level A):

- Initial midurethral sling surgery results in higher 1-year subjective and objective cure rates than pelvic floor physical therapy in women with stress urinary incontinence.
- Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension. Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings. Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings.
- There are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women.
- Burch colposuspension at the time of abdominal sacrocolpopexy and retropubic midurethral sling at the time of vaginal surgery for pelvic organ prolapse repair decrease the risk of postoperative stress urinary incontinence in women without preoperative stress urinary incontinence.

In my opinion TVT and TVTO are safe, effective, within the standard of care and are suitable first line surgical options with more support in the medical literature than any other MUS.¹⁰⁵ The TVT and TVTO devices are not defective and they have significant usefulness to surgeons in the field. The data does not support the theories that TVT and TVTO are cytotoxic, that they degrade or cause a harmful inflammatory response, that their pore size, weight, mechanical or laser cut or other features were harmful or cause significant clinical outcomes.

¹⁰⁵ 2015 Cochrane Review; 2014 AUGS/SUFU Statement; 2014 ACOG Statement; 2014 IUGA Statement; 2014 SGS Guidelines; 2013 AUA Position Statement; 2013 NICE Clinical Guideline 171; 2013 ICS SUI Fact Sheet; 2012 EAU Guideline; 2012 AUA Guideline; Cox 2013 Review; 2011 Cochrane Review; Novara 2010 metaanalysis.

I reserve the right to supplement or modify my expert opinion based on the discovery, disclosure and timely provision of new findings and the depositions of Plaintiffs' experts.

III. Fees & Testimony

My hourly charge is \$500.00 per hour.

In the past four years, I have given testimony as an expert in the following cases: Cavness v. Johnson & Johnson, et al., (9/30/2015 trial testimony) and Sandra Garcia v. Johnson & Johnson, Cameron County, TX Case No. 2013-DCL-3511-D (3/13/2015 deposition testimony).

A handwritten signature in dark ink, appearing to read "Jaime L. Sepulveda-Toro". The signature is fluid and cursive, with the last name being particularly prominent.

Jaime L. Sepulveda-Toro, M.D.

February 24, 2016